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A clinicopathological study and prognostic factor analysis of 177 salivary duct carcinoma patients from The Netherlands

Eline Boon ¹, Miranda Bel¹, Wim van Boxtel¹, Winette T. A. van der Graaf^{1,2}, Robert J. J. van Es³, Simone E. J. Eerenstein⁴, Robert J. Baatenburg de Jong⁵, Michiel W. M. van den Brekel⁶, Lilly-Ann van der Velden^{6,7}, Max J. H. Witjes⁸, Ann Hoebe⁹, Stefan M. Willems¹⁰, Elisabeth Bloemena¹¹, Laura A. Smit¹², Sjoukje F. Oosting¹³, PALGA Group, Marianne A. Jonker¹⁴, Uta E. Flucke¹⁵ and Carla M. L. van Herpen¹

¹ Department of Medical Oncology, Radboud University Medical Center, Nijmegen, The Netherlands

² The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, United Kingdom

³ Department of Head and Neck Surgical Oncology, University Medical Center Utrecht, Utrecht, The Netherlands

⁴ Department of Otorhinolaryngology/Head, Neck Surgery VU University Medical Center, Amsterdam, The Netherlands

⁵ Department of Otorhinolaryngology/Head and Neck surgery Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands

⁶ Department of Head and Neck Oncology and Surgery, Antoni van Leeuwenhoek/Netherlands Cancer Institute, Amsterdam, The Netherlands

⁷ Department of Otorhinolaryngology and Head and Neck surgery, Leiden University Medical Center, Leiden, The Netherlands

⁸ Department of Oral and Maxillofacial Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

⁹ Department of Medical Oncology, Maastricht University Medical Center, Maastricht, The Netherlands

¹⁰ Department of Pathology, University Medical Center Utrecht, Utrecht, The Netherlands

¹¹ Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands

¹² Department of Pathology, Antoni van Leeuwenhoek/Netherlands Cancer Institute, Amsterdam, The Netherlands

¹³ Department of Medical Oncology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

¹⁴ Department for Health evidence, Radboud University Medical Center, Nijmegen, The Netherlands

¹⁵ Department of Pathology, Radboud University Medical Center, Nijmegen, The Netherlands

Salivary duct carcinoma (SDC) is a subtype of salivary gland cancer with a dismal prognosis and a need for better prognostication and novel treatments. The aim of this national cohort study was to investigate clinical outcome, prognostic factors, androgen receptor (AR) and human epidermal growth factor receptor 2 (HER2) expression. SDC patients diagnosed between 1990 and 2014 were identified by the Nationwide Network and Registry of Histo- and Cytopathology in the Netherlands (PALGA). Subsequently, medical records were evaluated and pathological diagnoses reviewed. Data were analyzed for overall survival (OS), disease-free survival (DFS), distant metastasis-free survival (DMFS) and prognostic factors. AR was evaluated by immunohistochemistry (IHC), HER2 by IHC and fluorescent *in-situ* hybridization. A total of 177 patients were included. The median age was 65 years, 75% were male. At diagnosis, 68% presented with lymph node metastases and 6% with distant metastases. Median OS, DFS and DMFS were 51, 23 and 26 months, respectively. In patients presenting without distant metastases, the absolute number of positive lymph nodes was associated with poor OS and DMFS in a multivariable analysis. AR and HER2 were positive in 161/168 (96%) and 44/153 (29%) tumors, respectively, and were not prognostic factors. SDC has a dismal prognosis with primary lymph node involvement in the majority of patients. The absolute number of lymph node metastases was found to be the only prognostic factor for DMFS and OS. AR expression and—to a lesser extent—HER2 expression hold promise for systemic treatment in the metastatic and eventually adjuvant setting.

Key words: salivary duct carcinoma, salivary gland neoplasms, androgen receptors, receptor, ErbB-2, prognosis, survival, *in situ* hybridization, fluorescence, immunohistochemistry

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Conflict of Interest: S.F. Oosting

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Correspondence to: Prof. Dr Carla M. L. van Herpen, Department of Medical Oncology, Radboud University Medical Center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands, Tel.: +31-24-366-7251, E-mail: Carla.vanherpen@radboudumc.nl

What's new?

Salivary duct carcinoma (SDC) is a rare and often fatal malignancy. Little is known about associations between its pathological features and clinical outcome. In this study, clinicopathological factors were analyzed for 177 patients diagnosed with SDC in The Netherlands between 1990 and 2014. The data show that median overall survival (OS) and distant metastasis-free survival (DMFS) were 51 and 26 months, respectively. At diagnosis, 68% of patients presented with lymph node metastases. Lymph node positivity was associated with poor OS and poor DMFS. The absolute number of metastatic lymph nodes was the only significant prognostic factor for survival in a multivariate analysis. Androgen receptor and human epidermal growth factor 2 (HER2) were positive in 96% and 29%, respectively and were not a prognostic factor.

Salivary duct carcinoma (SDC) is a rare subtype of salivary gland cancer (SGC). It was first described in 1968,¹ and defined as a distinctive entity in 1990.² SDC usually affects middle-aged men and the tumor is often located in the parotid gland. Patients frequently present with locally advanced disease. Primary treatment consists of resection of the primary tumor and neck dissection, usually followed by radiotherapy. SDC is characterized by a high rate of distant metastases resulting in a limited overall survival (OS).³

Immunohistochemically, SDC resembles prostate cancer, because of common expression of the androgen receptor (AR).⁴ Androgen deprivation therapy (ADT) in a small series showed a 50% clinical benefit rate with a median duration of 12 months.⁵ Morphologically, SDC shows similarities with invasive ductal carcinoma of the breast. However, SDC only rarely shows estrogen and progesterone receptor expression.

Expression of the Human Epidermal Growth Factor Receptor 2 (HER2) was reported in 44% of 32 patients with SDCs.⁶

Due to the rarity of disease, only relatively small cohorts have been described and prognostic factors remain to be elucidated. The largest studies with 495 SDC patients based on the National Cancer Database (NCDB) and with 228 SDC patients based on the Surveillance, Epidemiology, and End Results Program (SEER) database, lack vital information on the occurrence of local and regional recurrences, distant metastases, the use of systemic therapy and AR or HER2 expression.³ Furthermore, no pathological review was performed in both studies.

Thanks to the unique collaboration between the Dutch Pathology Network PALGA and the national network of head and neck centers, we collected data of patients diagnosed with SDC in the Netherlands and aimed to evaluate clinicopathological characteristics (such as AR and HER2 expression and primary treatment) in relation to clinical outcome and prognostic factors.

Patients and Methods**Patient selection**

Patients diagnosed with SDC between 1990 and 2014 were identified by means of a retrospective search by the Nationwide Network and Registry of Histo- and Cytopathology in the Netherlands (PALGA).⁷ As all Dutch pathology laboratories participate in this network, all patients with a registered diagnosis of SDC in the Netherlands were enrolled. All patients were coded

by PALGA and clinical data could be correlated with the pathological features in a coded procedure.

Clinical data

Clinical data were collected from the medical records and were obtained with permission of treating physicians according to Dutch national laws and Good Clinical Practice. Review by a medical ethical committee was not obligatory by Dutch law due to the retrospective nature of the observations.

Pathology

For all patients, hematoxylin and eosin (H&E) stained slides, formalin-fixed paraffin-embedded (FFPE) tumor blocks and corresponding anonymous pathological reports were requested. All patient materials used in this study were obtained during routine patient care, and used for scientific research with permission by Dutch Law ("Code for Secondary Use of Human Tissue," Dutch Federation of Medical Scientific Societies). H&E slides were used for re-evaluation of the diagnosis and to mark areas of primary tumor by an experienced pathologist (UF). From each "donor" block, one to three cores of primary tumor were transferred into the "recipient" tissue micro array (TMA) block, using the TMA Grandmaster by Sysmex. From the new TMA "recipient blocks," slides were produced for further analysis. Each TMA slide was analyzed for AR and HER2 and scored by the pathologist (UF), who was blinded for the clinical outcome. AR (immunohistochemistry (IHC)) and HER2 (either IHC or fluorescent *in-situ* hybridization (FISH)) acquired during routine clinical care procedures was permitted in case it was not possible to determine AR or HER2 with a TMA. In case of heterogeneity between cores or between TMA and clinically obtained results, the highest score was used.

For AR expression, the AR polyclonal antibody of Santa Cruz was used, dilution 1:200, pretreatment with citrate (pH 6.0) for 10 min in a pretreatment module (Labvision/thermo scientific by Klinipath/VWR). Then, immunostaining was carried out with the detection system (Brightvision) of Immunologic, Duiven, the Netherlands. AR immunohistochemistry was executed in the Radboudumc. AR was scored positive or negative based on diffuse nuclear staining, as described in the WHO classification of SDC.⁸

HER2 was determined upfront by both IHC and FISH. The Hercepkkit of DAKO was used according to protocol for

HER2 immunostaining. For HER2 FISH, the probe of Kreatech (location of hybridization on 17q12cep17) was used. The probe was incubated according to standard ISH protocol. Scoring of HER2 was performed according to guidelines from the American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) analogous to breast cancer.⁹ HER2 IHC and FISH were scored independently. After scoring IHC and FISH, the results were compared. As the guideline does not mention how to report on discrepancies between IHC and FISH, we considered the result of HER2 FISH directive in discordant cases, that is, HER2 IHC3+ and HER2 FISH negative was scored as HER2 negative.

Definitions and statistical analysis

Lymph node ratio (LNR) was defined as the number of tumor-positive lymph nodes divided by the total number of lymph nodes resected. Date of diagnosis was defined as date of obtaining the first histological proof of SDC. In case the diagnosis was confirmed in a later stadium, the original date of obtaining the histopathological material was used. Overall survival (OS) was measured from date of diagnosis until death of any cause. Patients alive at last known follow-up date were censored. Disease-free survival (DFS) was measured from date of surgery until date of local or regional recurrence, distant metastases or death of any cause, whichever came first. Patients alive without disease at last known follow-up were censored. Distant metastasis free survival (DMFS) was defined as date of diagnosis until date of distant metastases or death of any cause, whatever came first. Patients alive without distant metastasis were censored. Survival curves were estimated with the Kaplan–Meier method. To investigate association between patient and tumor characteristics and survival, univariate Cox proportional hazards regression models were fitted first. Next, a multivariable Cox regression model was estimated with a forward selection procedure based on the Wald test at significance level of 0.05. The variables used in the multivariable analysis for OS and DMFS included gender, age (categorical), T- and N-stage, number of positive lymph nodes (categorical), AR, HER2, carcinoma ex pleomorphic adenoma, primary tumor site and resection margins. Patients with metastatic disease at diagnosis and patients with missing values in one or more of the variables were excluded from the multivariable analysis. Data were analyzed using SPSS version 22.0.

Results

Patient and tumor characteristics

Pathological review led to the inclusion of 177 eligible SDC patients out of 294 patients in the PALGA database (Fig. 1). Patient characteristics are shown in Table 1. The median age was 65 years [range 38–92], and the majority was male (75%). The parotid gland was the most affected (82%) salivary gland. Thirty-six percent of patients had an SDC arising from a pleomorphic adenoma (carcinoma ex pleomorphic

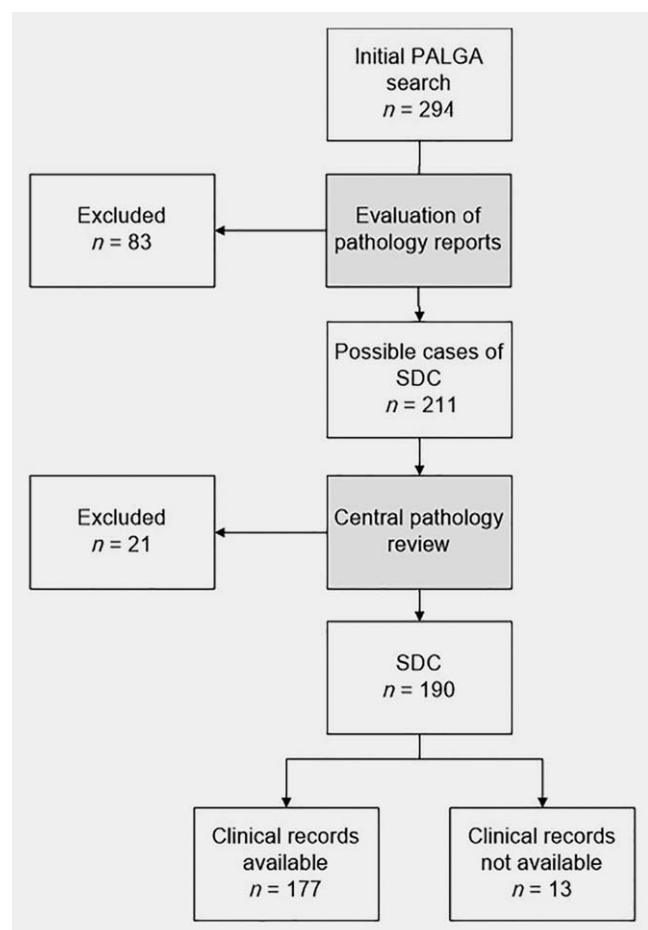


Figure 1. Consort diagram of inclusion of SDC patients. PALGA is the Nationwide Network and Registry of Histo- and Cytopathology in the Netherlands.

adenoma). One-hundred and twenty patients (68%) had lymph node metastases. Eleven patients (6%) presented with distant metastases. Ninety-six percent of 168 evaluable tumors were AR positive. Twenty-nine percent of the 153 evaluable tumors were HER2 positive. One-hundred and forty patients were evaluated for AR and HER2 using the TMA, the scores of the remaining patients were based on routine clinical evaluations. Table 2 shows the number of patients evaluated by FISH and IHC. Four patients had HER2 IHC3+ but had a negative HER2 FISH, and were scored as HER-2 negative.

Primary treatment with curative intent

Of the 177 patients, 162 patients underwent primary surgery with curative intent.

Fourteen patients did not have surgery because of an irresectable tumor in 3 patients or distant metastases at diagnosis in 11 patients. One patient underwent primary surgery of the primary tumor and neck dissection, but in retrospect had distant metastases on baseline imaging, and was not considered as having been treated with curative intent.

Table 1. Patient's and tumor characteristics

Characteristics	Number of patients (n = 177)
Median age, in years	65
Range, in years	38–92
Age, in years, n (%)	
≤ 50	19 (11)
51–60	43 (24)
61–70	54 (31)
71–80	41 (23)
> 80	20 (11)
Gender, n (%)	
Male	133 (75)
Female	44 (25)
Primary tumor, n (%)	
Parotid gland	145 (82)
Submandibular gland	19 (11)
Sublingual gland	2 (1)
Other	
Minor salivary glands	7 (4)
Lacrimal gland ¹	1 (1)
Unknown	3 (2)
Presenting symptoms, n (%)	
Painless mass	84 (48)
Painful mass	27 (15)
Facial nerve paralysis	51 (29)
Unknown	15 (9)
Carcinoma ex pleomorphic adenoma, n (%)	
Yes	63 (36)
No (“ <i>de novo</i> ”)	114 (64)
TNM stadium	
T1/T2/T3/T4/Tx	29/49/20/68/11
(%)	(16/28/11/38/6)
N0/N1/N2/N3	57/15/104/1
(%)	(32/8/59/1)
M0/M1	166/11
(%)	(94/6)
Overall stage	
I/II/III/IV/unknown	16/18/10/130/3
(%)	(9/10/5/73/2)
Primary treatment with curative intent² (n = 162)	
Surgery, n (%)	
Resection primary tumor with neck dissection	123 (76)
Resection primary tumor without neck dissection	36 (22)
Neck dissection only	3 (2)

Table 1. Patient's and tumor characteristics (Continued)

Characteristics	Number of patients (n = 177)
Postoperative radiotherapy, n (%)	
Yes	149 (91)
No	13 (9)
Neck dissection³	
Median number of resected lymph nodes, range	27 (1–122)
Median number of positive lymph nodes, range	4 (0–97)
Median lymph node ratio, range	0.20 [0–1.00]
Androgen receptor (AR), n (%)⁴	
Positive	162 (96)
Negative	6 (4)
HER2, n (%)⁵	
Positive	45 (29)
Negative	108 (71)
HER2 determination methods, n (%)	
FISH and IHC	140 (92)
FISH	5 (3)
IHC	8 (5)

¹Histopathological appearance of SDC despite its localization in the lacrimal gland.

²One patient underwent primary surgery despite distant metastases on baseline imaging in retrospect.

³n = 126 patients.

⁴Nine patients had no AR result. n = 168 patients.

⁵Twenty-four patients had no HER2 result. n = 153 patients.

Surgery. One hundred and sixty-two patients had primary surgery, of which 123 patients had a resection of the primary tumor and neck dissection, 36 patients only had a resection of the primary tumor. Three patients only underwent a neck dissection, because no primary tumor could be detected. In patients who underwent a neck dissection (n = 126), the median number of tumor positive lymph nodes was 4 [range 0–97] (Table 1). Figure 2 shows the number of tumor positive lymph nodes plotted against the total number of lymph nodes examined in the resected specimens (number of patients = 126). The median LNR was 0.20.

Radiotherapy. One hundred and forty-nine of 162 patients (91%) received postoperative radiotherapy. The median dose was 66 Gy (range 14–70 Gy). Only one of these patients underwent adjuvant concurrent chemoradiotherapy (CRT) (radiotherapy combined with weekly Cisplatin).

Patterns of recurrences and distant metastases

Eighty-seven out of 162 patients (54%) developed locoregional recurrence and/or distant metastases after primary treatment with curative intent. Figure 3a shows the Venn

Table 2. Univariate and multivariable analyses for overall survival and distant metastasis free survival

Factor	No of patients	Univariate			
		OS		DMFS	
		HR + 95% CI	<i>p</i>	HR + 95% CI	<i>p</i>
Increasing age in years	177	1.02 [1.00–1.03]	0.09	1.00 [0.99–1.02]	0.58
Age, categories ^{1,2}			0.31		0.67
≤50 years	19	1.00		1.00	
51–60 years	43	2.46 [1.01–6.00]	0.048	1.66 [0.83–3.30]	0.15
61–70 years	54	2.02 [0.83–4.95]	0.12	1.48 [0.74–2.93]	0.27
71–80 years	41	1.98 [0.79–4.98]	0.15	1.40 [0.69–2.83]	0.35
>80 years	20	2.74 [1.01–7.42]	0.048	1.24 [0.54–2.86]	0.62
Gender ^{1,2}					
Female	44	1.00		1.00	
Male	133	2.24 [1.24–4.06]	0.008	2.10 [1.27–3.49]	0.004
Carcinoma ex pleomorphic adenoma ^{1,2}					
No (“ <i>de novo</i> ”)	114	1.00		1.00	
Yes	63	0.80 [0.50–1.26]	0.33	0.88 [0.59–1.29]	0.50
T-stadium ^{1,2}			0.18		0.008
T1/T2	77	1.00		1.00	
T3/T4	89	1.50 [0.95–2.36]	0.08	1.88 [1.26–2.79]	0.002
Tx	11	1.56 [0.68–3.54]	0.29	1.65 [0.77–3.55]	0.20
N-stadium ^{1,2}					
N0	57	1.00		1.00	
N1/N2/N3	120	2.28 [1.36–3.81]	0.002	2.24 [1.44–3.49]	0.000
Number of positive lymph nodes ^{1,2}	159		0.000		0.000
0	56	1.00		1.00	
1–2	27	1.13 [0.54–2.40]	0.74	1.15 [0.60–2.23]	0.67
3–15	45	2.03 [1.11–3.72]	0.022	2.03 [1.20–3.45]	0.009
>15	31	3.83 [1.98–7.43]	0.000	4.38 [2.47–7.78]	0.000
Lymph node ratio (LNR)					
<0.20	64	1.00		1.00	
>0.20	60	2.43 [1.42–4.16]	0.001	2.36 [1.48–3.78]	0.000
M-stadium ³					
M0	166	1.00			
M1	11	4.26 [2.08–8.71]	0.000		
Resection margins ^{1,2}			0.31		0.57
Free	16	1.00		1.00	
Close	15	0.58 [0.17–1.92]	0.37	1.08 [0.44–2.66]	0.87
Tumor-positive margins	127	1.23 [0.59–2.59]	0.58	1.36 [0.70–2.64]	0.37
Primary tumor site ^{1,2}			0.90		0.96
Parotid gland	145	1.00		1.00	
Submandibular gland	19	0.85 [0.43–1.72]	0.66	0.93 [0.51–1.71]	0.82
Other	10	1.03 [0.44–2.39]	0.95	0.93 [0.43–2.02]	0.86
Androgenreceptor ^{1,2}					
Negative	6	1.00		1.00	
Positive	162	1.69 [0.53–5.39]	0.38	1.41 [0.52–3.86]	0.50
HER2 ^{1,2}					
Negative	108	1.00		1.00	
Positive	45	1.08 [0.65–1.81]	0.76	1.23 [0.80–1.89]	0.35

Factor	No of patients	Multivariable ³			
		OS		DMFS	
		HR + 95% CI	p	HR + 95% CI	p
Number of positive lymph nodes	136		0.003		0.000
0	49	1.00		1.00	
1–2	22	1.20 [0.50–2.86]	0.69	1.26 [0.60–2.66]	0.54
3–15	41	2.17 [1.09–4.32]	0.028	2.25 [1.25–4.06]	0.007
>15	25	3.96 [1.84–8.55]	0.000	4.73 [2.48–9.00]	0.000

Abbreviations: 95%CI, 95% confidence interval; DMFS, distant metastasis free survival; HR, hazard ratio; OS = overall survival.

¹Variables included in multivariable analyses for OS.

²Variables included in multivariable analyses for DMFS.

³Patients who presented with primarily metastatic disease were not included in the multivariable analysis.

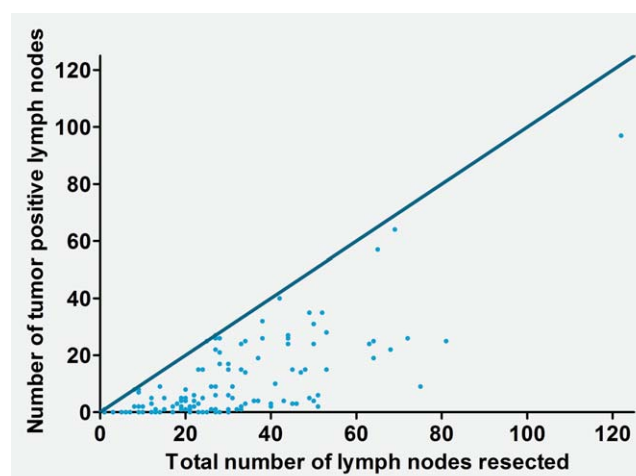


Figure 2. Tumor-positive lymph nodes are plotted against the total number of lymph nodes during neck dissection (number of patients = 126). The dark blue line represents the line at which all resected lymph nodes would have been tumor positive. [Color figure can be viewed at wileyonlinelibrary.com]

diagram of local, regional and distant recurrences in 162 patients treated with curative intent. Eighty-four out of 177 patients (47%) had distant metastases during the course of disease; 11 (6%) patients had distant metastatic disease at diagnosis and 73/162 (45%) patients developed distant metastases after primary treatment with curative intent. Figure 3b shows the sites of distant metastases for 84 patients who had distant metastases at diagnosis ($n = 11$) or developed distant metastases after treatment with curative intent ($n = 73$). Pulmonary (54%), bone (46%) and lymph nodes (42%) metastases were most frequently encountered. Brain metastases occurred in 15 (18%) patients. Of these 15 patients with brain metastases, the HER2 status was available in 13. Five out of 13 patients (38%) were HER2 positive, and the other 8 patients (62%) were HER2 negative. The median time until the occurrence of distant metastases was 16 months (range 1–69 months).

Treatment with palliative intent. In total, 84 patients had distant metastases (11 at time of diagnosis and 73 after

treatment with curative intent) and three patients had unresectable disease. One of these three patients received primary radiotherapy. The other two patients were treated with palliative ADT. Thirty-six patients with distant metastatic SDC received ADT as first- or second-line palliative treatment. Fifteen (18%) patients underwent chemotherapy and four (5%) patients targeted therapy. Most regimens included either taxanes (docetaxel or paclitaxel) or platinum (cisplatin or carboplatin) based chemotherapy. Some patients received multiple lines of systemic therapy. Forty-four (54%) of 84 patients with distant metastases received only best supportive care. A total of 39 (46%) patients with distant metastases underwent radiotherapy with palliative intent.

Survival

After a median follow-up of 26 months, 84 of 177 patients had died. The 5- and 10-years survival were estimated as 43% [95% CI 33–52%] and 26% [95%CI 15–37%], respectively. The 5- and 10-year DFS were estimated as 28% [95% CI 20–36%] and 17% [95% CI 8–25%], respectively. The 5- and 10-year DMFS were 32% [95% CI 24–40%] and 20% [95% CI 2–29%], respectively.

Estimates for the median OS, DFS and DMFS were 51 months (95% CI 40–61 months), 23 months (95% CI 18–27 months) and 26 months (95% CI 20–34 months), respectively. The Kaplan–Meier curves for OS, DFS and DMFS are shown in Figures 4a–4c.

Prognostic factors

Patient selection. All 177 patients were included in the univariate analysis. Patients with distant metastases at diagnosis were not included in multivariable analyses for OS and DMFS. Owing to missing values, only 136 patients were included in the multivariable predictive model for OS and DMFS.

Overall survival. Univariate analysis showed that male gender, high N-stadium, increasing number of tumor positive lymph nodes, LNR and primarily metastatic disease at diagnosis were associated with poor OS. The multivariable

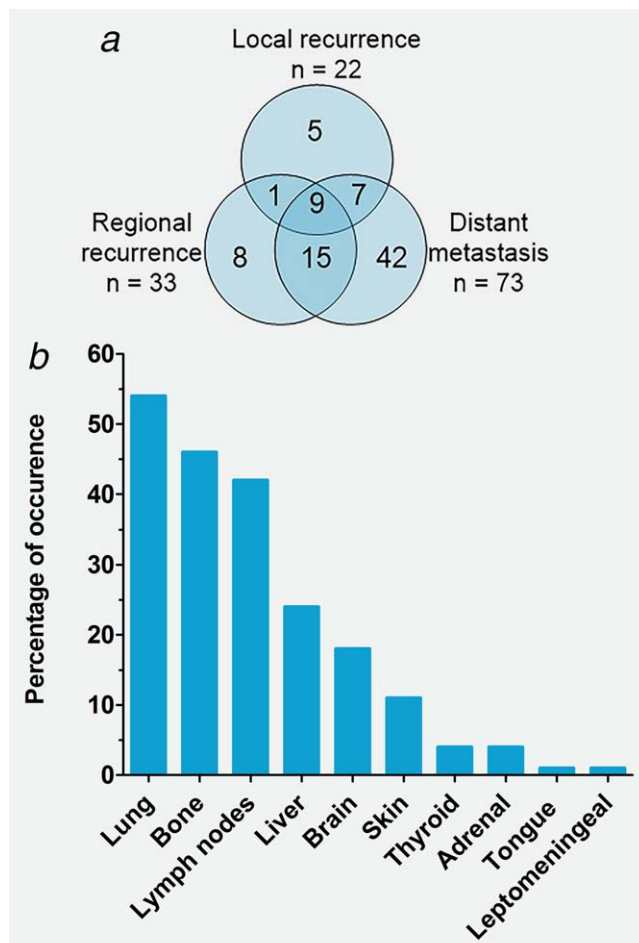


Figure 3. Patterns of disease recurrence. (a) Breakdown of local and regional recurrences and distant metastases in 87 patients with a recurrence. The numbers in the circles represent the absolute number of patients with local and regional recurrences and the presence of distant metastases. Patients with primarily metastatic disease are not included in this figure. (b) Localization of distant metastases sorted by percentage of presence in 84 patients with distant metastases. Patients with primarily metastatic disease were included in this figure. [Color figure can be viewed at wileyonlinelibrary.com]

prediction model only contained the number of positive lymph nodes as independent variable: an increasing number of positive lymph nodes negatively affects survival (overall $p = 0.003$) (3–15 lymph nodes vs. 0 lymph nodes HR 2.17, 95% CI 1.09–4.32, $p = 0.028$; >15 lymph nodes vs. 0 lymph nodes HR 3.96, 95% CI 1.84–8.55, $p = 0.000$). The number of lymph nodes was categorized due to a nonlinear correlation with OS.

No significant association was found between AR and HER2 and OS in the univariate as well as the multivariable analysis. The results of the univariate and multivariable analyses for OS are shown in Table 2.

Distant metastasis free survival. Male gender, high T-stadium, high N-stadium, increasing numbers of positive lymph nodes and LNR were associated with poor DMFS

using univariate analysis. The final multivariable prediction model only contained the number of positive lymph nodes as independent variable; an increasing number of positive lymph nodes is a prognostic factor for poor DMFS (overall $p = 0.000$) (3–15 lymph nodes vs. 0 lymph nodes HR 2.25, 95% CI 1.25–4.06, $p = 0.007$; >15 lymph nodes vs. 0 lymph nodes HR 4.73, 95% CI 2.48–9.00, $p = 0.000$). The number of lymph nodes was categorized due to nonlinear correlation with DMFS. From the univariate and multivariable analysis, no significant association was found between DMFS and AR and HER2. The results of the univariate and multivariable analysis for DMFS are displayed in Table 2.

Discussion

In this article, we present 177 patients with SDC, which represents the largest series of SDC patients with pathological review worldwide. These data provide extensive insight in treatment, clinical outcome, AR and HER2 expression/amplification and prognostic factors in SDC patients. This study underscores the aggressive clinical course characterized by a high rate of distant metastases (47%), and a median OS of 51 months. AR and HER2 were positive in 96 and 29% respectively; both were of no prognostic value as they were not significantly associated with OS and DMFS. The number of positive lymph nodes was the only factor independently associated with poor OS and DMFS.

SDC has a high propensity for lymph node and distant metastases; 68% of our patients presented with lymph node metastases, which is higher than the 46.6% and 49% reported by Osborn and Jayaprakash *et al.*^{3,10} An abundance of tumor positive lymph nodes was observed in neck dissections. Furthermore, distant metastases were observed relatively short after primary diagnosis with a median time until distant metastases of only 16 months. Although distant metastases occurred mostly in the lungs, bones and lymph nodes, a wide variety of metastatic sites were seen, of which the 18% rate of brain metastasis was most notable. Local and regional recurrences were often accompanied by distant metastases. In this study, 67% of patients with a local or regional recurrence also had distant metastases, as shown in Figure 3a, which corresponds to the 23–75% found in two other reports.^{11,12} Therefore, in case of local or regional recurrences, we suggest thorough screening for distant metastases, as this may change treatment from curative to palliative intent. Moreover, despite locoregional control, distant metastases were encountered during follow-up in 42 patients. Notably, 54% of patients with metastatic disease did not receive any form of systemic treatment. Possible explanations for this may be the extensiveness of disease, performance status, co-morbidity and unfamiliarity of physician with the treatment of this rare tumor type, especially during the early years of the time period that we have studied. This may have influenced the overall survival of SDC patients in general.

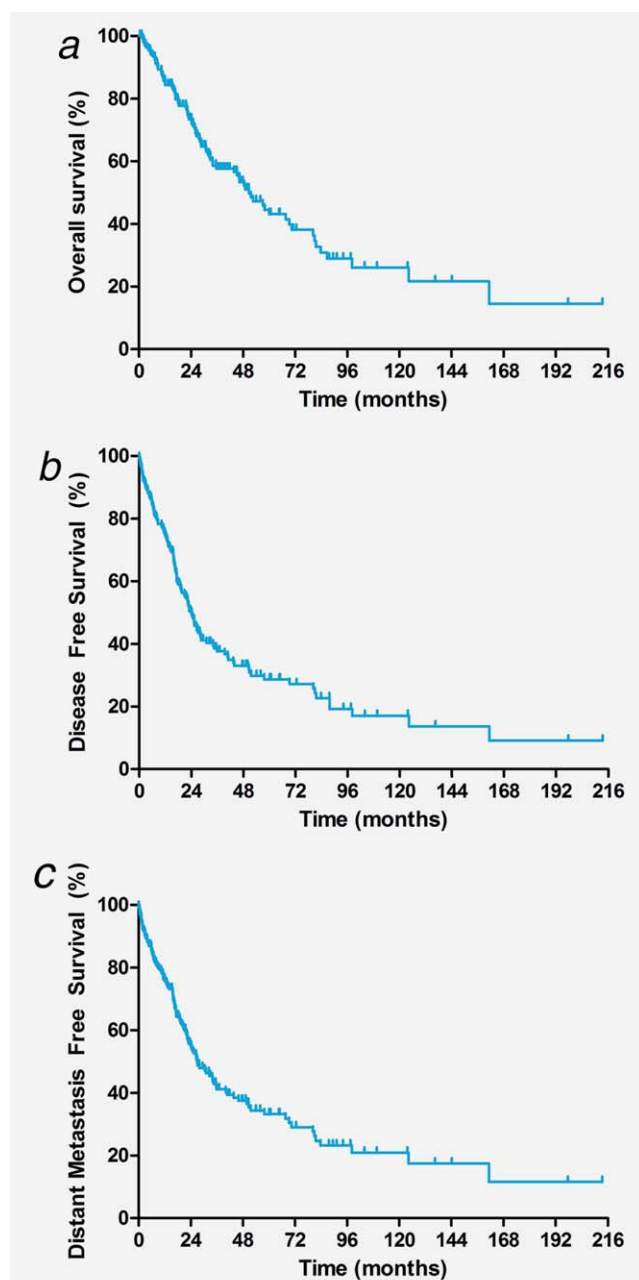


Figure 4. Kaplan–Meier curves for overall survival (OS), disease-free survival (DFS) and distant metastasis free survival (DMFS) based on data of 177 SDC patients. (a) Kaplan–Meier curve for OS based on data of 177 SDC patients. Estimated median OS was 51 months (95% CI 40–61 months). (b) Kaplan–Meier curves for DFS based on data of 177 SDC patients. Estimated median DFS was 23 months (95% CI 18–27 months). (c) Kaplan–Meier curve of DMFS based on data of 177 SDC patients. Estimated median DMFS was 26 months (95% CI 20–34 months). [Color figure can be viewed at wileyonlinelibrary.com]

Recently, a few cohort studies on patients with SDC were published. The cohort based on the National Cancer Database (NCDB) is the largest cohort of SDC patients with 495 patients (no median OS described for all patients) followed by the SEER database with 228 patients (median OS 79

months).^{3,10} However, lack of pathology review has a risk of including patients with other diagnosis as the histological diagnosis of SDC is notoriously difficult. The median OS in this study (51 months) was comparable to a cohort study of 56 patients in a single institution in Korea (OS of 48 months).¹³ In a Japanese study with 141 SDC patients, where all tumors were pathologically reviewed, three-year OS was 73% *versus* 57% in our series.¹¹

In our series, 96% of tested tumors had a positive AR. This is comparable with other series of SDC patients reporting AR positivity up to 89%.⁴ AR positivity, in the presence of typical morphological features, is strongly suggestive for SDC, although other subtypes of SGC may express AR.¹⁴ ADT is an interesting therapeutic option for AR-positive SDC.⁵ The results of first-line ADT in our patients will be published in a separate article.¹⁵

We confirmed the presence of HER2 in 29% of tested cases, which is in line with the previously described HER2 amplification/expression in 27% (of 41), 32% (of 31) and 44% (of 32) SDC cases.^{6,16,17} We reported on four patients with HER2 IHC3+ with HER2 FISH-negative tumor samples. Although this is unusual, it is known from comparative studies that this may occur.¹⁸ Recently, preliminary data for 45 patients with HER2-positive advanced unresectable SGC (of the ductal subtype) treated with docetaxel and trastuzumab in a phase 2 trial showed promising results, that is, overall response rate of 69%, median PFS of 11.3 months and median OS of 38.0 months.¹⁹ These results seem to support treating HER2-positive SDC patients with trastuzumab plus docetaxel.

Unfortunately, it was not possible to correlate clinical outcomes to other genetic alterations such as TP53 and PI3KCA. Future research may include characterization of genetic alterations and clinical outcomes of SDC patients.

Studies demonstrated a correlation between lymph node metastases and OS. There seems to be no consensus on the best way of categorizing lymph node metastases, whereby classifications comparing N0–1 *versus* N2–3, N2b–c *versus* N0–N2a or N0 *versus* any N+ disease are used.^{3,12,13,20} We demonstrated in the univariate analysis that lymph node metastases is indeed a significant prognostic factor. However, in the multivariable analysis, the absolute number of tumor positive lymph nodes is a stronger prognostic factor than the N-stage and LNR.²¹ We therefore suggest a categorizing system according to the absolute number of tumor positive lymph nodes (categorized as 0, 1–2, 3–15 and >15 lymph nodes), although this needs to be validated in other SDC cohorts.

One may argue if the patient with SDC of the lacrimal gland should be included in the analysis; however, the histopathological features in this particular patient included comedo-type necrosis and AR positivity. Recently, another case of AR-positive SDC of the lacrimal gland was described in literature.²²

The main strengths of this study are the large number of patients data collected using a nationwide search strategy by PALGA, which covers 95–100% of all cancer patients, and especially the pathological review of SDC cases. A major advantage of our data, as compared to the larger, national NCDB and SEER databases, is the availability of individual patient data in our cohort. Extensive data on diagnosis, treatment, recurrence patterns and survival could be collected and has given valuable insights not only in the presentation but also in the course of the disease. We were therefore able to analyze meaningful prognostic factors in univariate and multivariable analyses. Limitations of this study are mainly due to its' retrospective nature, the absence of FFPE blocks for AR and HER2 testing in some cases, and a not 100% coverage of all detailed information. Only tumors classified as SDC were included; therefore, patients that may have been wrongfully classified, that is, as another subcategory of the SGCs, may have been missed.

In conclusion, we presented 177 SDC patients with pathological review of the diagnosis. The median OS was just over 4 years, and the disease was characterized by a high initial lymph node involvement and development of a high rate of distant metastases. In the multivariable analysis, the absolute number of positive lymph nodes was the only significant prognostic factor for both poor OS and DMFS. We advocate

the determination of AR and HER2 as this may have therapeutic consequences, although these are not prognostic factors. Given the high recurrence rate, future clinical research could encompass adjuvant treatment in high-risk lymph node-positive patients.

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Pathologist	Affiliation
J. Meijer	Rijnstate Hospital, Arnhem, The Netherlands
J.E. van der Wal	Martini Hospital, Groningen, The Netherlands
L. Arensman	Meander MC, Amersfoort, The Netherlands Tissue Bank, University Medical Center, Groningen, The Netherlands Stichting laboratorium Pathologie Oost-Nederland

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